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	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L1	Fitzgerald.in.	4239
☐	L2	L1 and pe	147
☐	L3	L1 and exotoxin	71
☐	L4	l1 and ib	70
☐	L5	L4 and exotoxin	21
☐	L6	L4 and pseudomonas	22
☐	L7	L6 or l5	22
	DB=USPT; PLUR=YES; OP=OR		
☐	L8	US-N6911227-N.did.	0
	DB=USPT,PGPB; PLUR=YES; OP=OR		
☐	L9	(US-N6911227-N)![pn]	0
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☐	L10	6911227	1

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Kreitman, R.J. et al., "Rational Design of a Chimeric Toxin: An Intramolecular Location for the Insertion of Transforming Growth Factor .alpha. within Pseudomonas Exotoxin as a Targeting Ligand", Bioconjugate Chemistry, pp. 58-62 (1992).

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END OF SEARCH HISTORY

L7: Entry 6 of 22 File: USPT Jul 30, 2002

US-PAT-NO: 6426075
DOCUMENT-IDENTIFIER: US 6426075 B1

TITLE: Protease-activatable pseudomonas exotoxin A-like proproteins

DATE-ISSUED: July 30, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fitzgerald; David J.	Rockville	MD		
Reiter; Yoram	Ness Ziona			IL
Pastan; Ira	Potomac	MD		

US-CL-CURRENT: 424/260.1; 424/183.1, 424/184.1, 424/192.1, 424/193.1, 424/236.1, 424/261.1, 435/69.1, 435/69.7, 435/71.1 , 435/71.3, 530/356, 530/387.3, 530/391.7

CLAIMS:

What is claimed is:

1. A protease-activatable Pseudomonas exotoxin A-like ("PE-like") proprotein comprising: (a) a cell recognition domain that binds to an exterior surface of a targeted cell; (b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence is refractory to cleavage by furin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25.degree. C. for 16 hour; (c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ ID NO:2, the cytotoxicity domain having ADP-ribosylating activity; and (d) an endoplasmic reticulum ("ER") retention sequence.

2. The PE-like proprotein of claim 1 wherein the modified PE translocation domain has a PE domain II sequence (amino acids 253-364 of SEQ ID NO:1) modified with amino acids substitutions introducing the protease activatable sequence so as to cause cleavage by the protease between amino acids 279 and 280.

3. The PE-like proprotein of claim 1 wherein the protease activatable sequence is cleavable by a protease secreted by a cancer cell.

4. The PE-like proprotein of claim 1 wherein the cell recognition domain comprises an antibody that specifically binds to a cancer cell surface marker.

5. The PE-like proprotein of claim 2 wherein the protease activatable sequence

is cleavable by prostate specific antigen ("PSA").

6. The PE-like proprotein of claim 2 wherein the protease activatable sequence is cleavable by urokinase.

7. The PE-like proprotein of claim 2 wherein the protease activatable sequence is cleavable by neutral endoprotease, stromelysin, collagenase, cathepsin B, or cathepsin D.

8. The PE-like proprotein of claim 2 further comprising a PE Ib domain, and wherein said PE Ib domain, the cytotoxicity domain, and the ER retention sequence together have the sequence of domains Ib and III of native PE.

9. The PE-like proprotein of claim 3 wherein the cell recognition domain is coupled to the modified translocation domain through a peptide bond.

10. The PE-like proprotein of claim 5 wherein the protease activatable sequence is SKGSFSIQYTYHV (SEQ ID NO:11), HLGGSQQLLHNKQ (SEQ ID NO:12), or SKGKGTSSQYSNTE (SEQ ID NO:13).

11. The PE-like proprotein of claim 6 wherein the protease activatable sequence is DRVYIHPF (SEQ ID NO:3), VVCGERGFFYTP (SEQ ID NO:4), FFYTPKA (SEQ ID NO:5), KRRPVKVYP (SEQ ID NO:6), PVGKKRRPVKVY (SEQ ID NO:7), KPVGKKRRPVKV (SEQ ID NO:8), GKPVGKKRRPVK (SEQ ID NO:9), or TFAGNAVRRSVGQ (SEQ ID NO:10).

12. The PE-like proprotein of claim 8 wherein the cell recognition domain is an antibody coupled to the modified translocation domain through a peptide bond and wherein the antibody specifically binds a cancer cell surface marker.

13. A composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a protease-specific Pseudomonas exotoxin A-like ("PE-like") proprotein comprising: (a) a cell recognition domain that binds to an exterior surface of a targeted cell; (b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence is substantially un-activatable by fibrin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25.degree. C. for 16 hours; (c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ WD NO:2, the cytotoxicity domain having ADP-ribosylating activity; and (d) an endoplasmic reticulum ("ER") retention sequence.

14. The composition of claim 13, further comprising a PE Ib-like domain, wherein: (a) the cell recognition domain is an antibody coupled to the modified PE translocation domain through a peptide bond and wherein the antibody specifically binds a cancer cell surface marker; (b) the modified PE translocation domain has a PE domain II sequence (amino acids 253-364 of SEQ ID NO:1) modified with amino acids substitutions introducing the protease activatable sequence so as to cause cleavage by the protease between amino acids 279 and 280; and (c) the PE Ib-like domain, the cytotoxicity domain and the ER retention sequence together have the sequence of domains Ib and III of native PE.

15. The composition of claim 14 wherein the protease activatable sequence is

cleavable by prostate specific antigen or urokinase.

16. A method for killing a cancer cell comprising contacting the cell with a protease-specific Pseudomonas exotoxin A-like ("PE-like") proprotein comprising: (a) a cell recognition domain that binds to an exterior surface of a targeted cell; (b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence cysteine-cysteine loop is substantially un-activatable by furin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25.degree. C. for 16 hours; (c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ ID NO:2, the cytotoxicity domain having ADP-ribosylating activity; and (d) an endoplasmic reticulum ("ER") retention sequence.

17. The method of claim 16 wherein the cancer cell is a prostate cancer cell.

18. The method of claim 16 wherein the cancer cell is a colon cancer cell.

19. The method of claim 16 used in the treatment of a subject suffering from cancer.

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L4: Entry 2 of 10 File: PGPB Apr 14, 2005

PGPUB-DOCUMENT-NUMBER: 20050079171
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050079171 A1

TITLE: Pseudomonas exotoxin A-like chimeric immunogens for eliciting a secretory IgA-mediated immune response

PUBLICATION-DATE: April 14, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
FitzGerald, David J.	Rockville	MD	US
Mrsny, Randall J.	Redwood City	CA	US

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
The Government of the USA as represented by the Secretary of the Dept. of Health & Human Services	Rockville	MD		02
Genentech, Inc.	South San Francisco	CA		02

APPL-NO: 10/659036 [PALM]
DATE FILED: September 9, 2003

RELATED-US-APPL-DATA:
Application 10/659036 is a continuation-of US application 09/462713, filed May 12, 2000, ABANDONED
Application 09/462713 is a a-371-of-international WO application PCT/US98/14336, filed July 10, 1998, PENDING
Application is a non-provisional-of-provisional application 60/056924, filed July 11, 1997,

INT-CL-PUBLISHED: [07] A61 K 39/395

US-CL-PUBLISHED: 424/133.1
US-CL-CURRENT: 424/133.1

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

This invention provides methods of eliciting a secretry IgA-mediated immune response in a subject by administering a Pseudomonas exotoxin A-like chimeric immunogens that include a non-native epitope in the Ib domain of Pseudomonas exotoxin. Compositions comprising secretory IgA antibodies that specifically

recognize an epitope of HIV-1 also are provided.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of the filing date of co-pending application 60/056,924, filed Jul. 11, 1997, the content of which is incorporated herein by reference in its entirety.

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DOCUMENT-IDENTIFIER: US 20040247617 A1
TITLE: Fusion antigen used as vaccine

CLAIMS:

1. A fusion antigen specific for a target cell comprising: an antigenic moiety; a ligand moiety which is capable of reacting, recognizing or binding to a receptor on the target cell; a Pseudomonas exotoxin A translocation domain II; and a carboxyl terminal moiety which permits retention of the fusion antigen in the endoplasmic reticulum (ER) membrane of the target cell.

2. The fusion antigen according to claim 1, wherein the target cell is an antigen presenting cell.

3. The fusion antigen according to claim 1, wherein the target cell is selected from the group consisting of T-cells, B-cells, dendritic cells, monocytes, and macrophages.

14. The pharmaceutical composition according to claim 13 is a T-cell vaccine.

15. A method of immunizing an animal comprising the steps of: (a) providing a fusion antigen specific for a target cell comprising an antigenic moiety, a ligand moiety which is capable of reacting, recognizing or binding to a receptor on the target cell, a Pseudomonas exotoxin A translocation domain II, and a carboxyl terminal moiety which permits retention of the fusion antigen in the endoplasmic reticulum (ER) membrane of the target cell; and (b) inoculating the fusion antigen into the animal.

16. The method according to claim 15, wherein the target cell is an antigen presenting cell.

23. The method according to claim 15, wherein the target cell is selected from the group consisting of T cell, B cell, dendritic cell, monocyte, and macrophage.

27. A fusion porcine reproductive and respiratory syndrome virus (PRRSV) ORF 7 antigen comprising a PRRSV ORF 7 moiety; a Pseudomonas exotoxin A binding domain I; a Pseudomonas exotoxin A translocation domain II; and a carboxyl terminal moiety which permits retention of the fusion antigen in the endoplasmic reticulum (ER) membrane of a target cell.

28. The fusion antigen according to claim 27, wherein the target cell is an antigen presenting cell.

29. The fusion antigen according to claim 27, wherein the target cell is selected from the group consisting of T cell, B cell, dendritic cell, monocyte, and macrophage.

35. The pharmaceutical composition according to claim 34 is a T-cell vaccine.

36. A method of immunizing an animal for the preventing porcine reproductive and respiratory syndrome virus (PRRSV), which comprises the steps of: (a) providing a fusion antigen comprising a PRRSV ORF 7 antigen moiety, a Pseudomonas exotoxin A binding domain I, a Pseudomonas exotoxin A translocation domain II, and a carboxyl terminal moiety which permits retention of the antigen in the endoplasmic reticulum (ER) membrane of a target cell; and (b) inoculating the fusion antigen into the animal.

37. The method according to claim 36, wherein the target cell is an antigen presenting cell.

38. The method according to claim 36, wherein the target cell is selected from the group consisting of T-

cells, B-cells, dendritic cells, monocytes, and macrophages.

DOCUMENT-IDENTIFIER: US 6498233 B1
TITLE: Nucleic acid transfer system

CLAIMS:

1. A multidomain protein comprising, a target cell-specific binding domain, a translocation domain and a nucleic acid binding domain, wherein the translocation domain is derived from a diphtheria toxin but does not include the cytotoxic part of said diphtheria toxin, wherein the translocation domain is derived from amino acids 194-378 or 196-384 of said diphtheria toxin.

2. The multidomain protein according to claim 1, wherein said translocation domain is amino acids 194-378 or 196-384 of said diphtheria toxin.

3. The multidomain protein according to claim 1, further comprising an endoplasmic reticulum retention signal and a nuclear localization signal, wherein said protein has an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:35, SEQ ID NO:37, and SEQ ID NO:39.

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L7: Entry 2 of 22 File: PGPB Apr 14, 2005

cite

PGPUB-DOCUMENT-NUMBER: 20050079171
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050079171 A1

TITLE: Pseudomonas exotoxin A-like chimeric immunogens for eliciting a secretory IgA-mediated immune response

PUBLICATION-DATE: April 14, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
FitzGerald, David J.	Rockville	MD	US
Mrsny, Randall J.	Redwood City	CA	US

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
The Government of the USA as represented by the Secretary of the Dept. of Health & Human Services	Rockville	MD		02
Genentech, Inc.	South San Francisco	CA		02

APPL-NO: 10/659036 [PALM]
DATE FILED: September 9, 2003

RELATED-US-APPL-DATA:
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Application 09/462713 is a a-371-of-international WO application PCT/US98/14336, filed July 10, 1998, PENDING
Application is a non-provisional-of-provisional application 60/056924, filed July 11, 1997,

INT-CL-PUBLISHED: [07] A61 K 39/395

US-CL-PUBLISHED: 424/133.1
US-CL-CURRENT: 424/133.1

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

This invention provides methods of eliciting a secretry IgA-mediated immune response in a subject by administering a Pseudomonas exotoxin A-like chimeric immunogens that include a non-native epitope in the Ib domain of Pseudomonas exotoxin. Compositions comprising secretory IgA antibodies that specifically

recognize an epitope of HIV-1 also are provided.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of the filing date of co-pending application 60/056,924, filed Jul. 11, 1997, the content of which is incorporated herein by reference in its entirety.

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US-PAT-NO: 5328984
DOCUMENT-IDENTIFIER: US 5328984 A
** See image for Certificate of Correction **

TITLE: Recombinant chimeric proteins deliverable across cellular membranes into cytosol of target cells

DATE-ISSUED: July 12, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira H.	Potomac	MD		
Trevor; Prior	Bethesda	MD		
Fitzgerald; David J.	Silver Spring	MD		
Debinski; Waldemar	Gaithersburg	MD		
Siegall; Clay	Silver Springs	MD		

US-CL-CURRENT: 424/134.1; 435/69.7, 530/350, 530/387.3, 530/399, 530/402, 536/23.4

CLAIMS:

What is claimed is:

1. A chimeric protein of which a portion is translocated across a cellular membrane into the cytosol of target cells, the chimeric protein comprising, linked together at least (1) a first segment comprising a foreign protein desired to be introduced into the cytosol of the target cells, (2) a second segment from Domain II of Pseudomonas exotoxin having a translocation function which delivers the foreign protein across the cellular membrane into the cytosol of the target cells, and (3) a third segment which binds the chimeric protein to the target cells, the foreign protein being otherwise impermeable to the target cells and heterologous to the second segment.

2. The chimeric protein of claim 1, wherein said third segment is a ligand, an antibody, a growth factor or a cytokine for selective recognition of target cells.

3. The chimeric protein of claim 1, being PE-Bar.

4. The chimeric protein of claim 1, being PE.sup..DELTA..sbsp.553 -Bar.

5. A DNA molecule having a sequence that encodes the chimeric protein of claim 1.

6. A method for introducing a foreign protein across a cellular membrane into the cytosol of target cells, comprising the step of contacting cells into which a foreign protein is desired to be introduced, with the chimeric protein of claim 1.

7. A composition comprising an effective amount of the chimeric protein of claim 1 and pharmaceutically acceptable carrier.

8. A chimeric protein comprising:

a first segment comprising a foreign protein;

a second segment from Domain II of Pseudomonas exotoxin which translocates the first segment across a cellular membrane; and

a third segment which binds the chimeric protein to a target cell;

wherein the foreign protein is heterologous to the second segment.

9. The chimeric protein of claim 8, wherein the third segment is a ligand, an antibody, a growth factor or a cytokine.

10. The chimeric protein of claim 8, wherein the third segment is Domain Ia of Pseudomonas exotoxin.

11. The chimeric protein of claim 8, wherein the foreign protein is selected from the group consisting of barnase and somatostatin.

12. A DNA molecule sequence that encodes a chimeric protein having a foreign protein segment, a segment from Domain II of Pseudomonas exotoxin that has a translocation function which delivers the foreign protein across cellular membranes into the cytosol of target cells all linked to a third segment which encodes a protein that binds the chimeric protein to the target cells, the foreign protein being otherwise impermeable to the target cells and heterologous to the protein having the translocation function.

13. A method of making a translocatable chimeric protein, comprising the step of making a chimeric gene by linking together at least (1) a foreign protein gene sequence that encodes a foreign protein desired to be introduced into the cytosol of a target cell, (2) a heterologous gene sequence from a sequence encoding Domain II of Pseudomonas exotoxin that encodes a protein having a translocation function which delivers the foreign protein across the cellular membrane into the cytosol of the target cell, and (3) a gene sequence encoding a protein which binds the chimeric protein to the target cell, then allowing the expression of said chimeric gene in a suitable expression system so that a translocatable chimeric protein is obtained, and then recovering said chimeric protein from said expression system.

US-PAT-NO: 5082927
DOCUMENT-IDENTIFIER: US 5082927 A

TITLE: Selectively cytotoxic IL-4-PE40 fusion protein

DATE-ISSUED: January 21, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pastan; Ira	Potomac	MD		
FitzGerald; David	Silver Spring	MD		
Ogata; Masato	Rockville	MD		

US-CL-CURRENT: 530/351; 424/192.1, 424/85.1, 424/85.2, 435/4, 435/69.5, 435/69.52, 435/71.3, 514/2, 514/8, 530/402, 530/403, 530/404, 530/405, 530/406, 530/820, 530/825

CLAIMS:

What is claimed is:

1. A functionally active recombinant IL-4-PE40 fusion protein that selectively kills cells bearing IL-4 receptors, without killing cells lacking IL-4 receptors, wherein the fusion protein has ADP ribosylating properties.

2. The recombinant fusion protein of claim 1 produced by employing plasmid pM048 in an expression vector.

3. A composition, comprising an effective amount of the recombinant fusion protein of claim 1 and pharmaceutically acceptable carrier.

4. A mutant form of the fusion protein of claim 1 which consist of IL-4-PE40 Asp.sup.553.